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Primary and Secondary Osteosarcoma of the Face: A Rare Childhood Malignancy

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Background. Osteosarcoma of the head and neck, especially primary forms, remains a rare and highly malignant tumor

Patients. This report describes two patients who developed an osteosarcoma of the face more than ten years after treatment for bilateral retinoblastoma. We also report a third patient who presented with a primary osteosarcoma of the right superior maxilla which is one of the rarest tumors encountered in childhood oncology.

Conclusions. The mainstay of therapy is surgical resection with negative margins. Careful, long-term follow-up of survivors of hereditary retinoblastoma is essential, especially for those given radiation therapy. Med. Pediatr. Oncol. 30:170–174, 1998. © 1998 Wiley-Liss, Inc.

Key words: retinoblastoma; osteosarcoma; face; head and neck cancer

INTRODUCTION

Osteosarcoma is a malignant bone tumor arising from primitive boneforming mesenchyma. It is characterized by the production of osteoid tissue or immature bone by malignant proliferating spindle cell stroma. It occurs most frequently during the pubertal growth spurt, affecting primarily the metaphyses of the distal femur, the proximal tibia and humerus and rarely the orbital or facial area [1].

We report three patients with osteosarcoma of the face. The first two patients presented with secondary osteosarcomas after having previously been treated for bilateral retinoblastomas. The third patient developed a primary osteosarcoma of the right upper maxilla, one of the rarest tumors encountered in childhood oncology.

Case Reports

Case 1. This girl was found to have bilateral retinoblastoma when she was 9 months of age. There was no family history of retinoblastoma. Her constitutional chromosome analysis showed normal findings on southern blot (see materials and methods). She underwent an unilateral enucleation of her right eye which showed an invaded optic nerve and a tumor mass. Retinoblastoma of mixed histology was confirmed. Her left eye showed three localisations of retinoblastoma: one was cryocoagulated and the other two were treated with external-beam radiation therapy (3.900 cGy in 13 fractions over 41 days) after one course of combination chemotherapy: doxorubicin 40 mg/m^2, vincristine 1.5 mg/m^2 and cyclophosphamide 300 mg/m^2. Radiation therapy was followed by another 9 courses of 3-weekly triple chemotherapy until the cumulative dose of 480 mg/m^2 doxorubicin was reached. Vincristine and cyclophosphamide were continued for a total of 17 courses.

Eleven years after the initial diagnosis of retinoblastoma was made, she presented with a history of increasing pain and a soft tissue mass of her left cheek as well as left epistaxis. Contrast-enhanced computed tomography (CT-scan) and magnetic resonance imaging (MRI) of the maxilla showed a tumor mass (Fig. 1). On technetium-99m methylene diphosphonate (MDP) bone scintigraphy, increased activity in the left upper maxillary region was present. Chest X-ray films, CT-scan of the thorax and echocardiography were normal. The diagnosis of osteosarcoma was made by a biopsy. She received six courses of chemotherapy combining doxorubicin 25 mg/m^2 (day 1, 2 & 3) and cisplatin 100 mg/m^2 (day 1). A left maxillectomy was performed after three courses of chemotherapy. The response rate was poor: the tumour was still viable and the edges were unfortunately not free of malignant cells. She is alive without progressive disease 5 months after stopping chemotherapy.

Case 2. This boy without relevant family history had bilateral retinoblastoma when he was 2 and a half months old for which he was treated in another hospital. He underwent an unilateral enucleation of his left eye and

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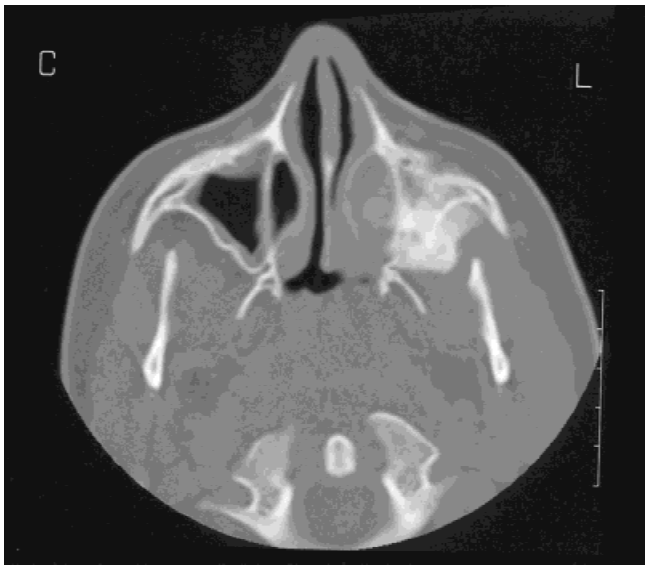

Fig. 1. Contrast-enhanced computed tomography (CT scan) of the maxilla of Case 1, showing tumor mass with focal bone destruction of the left maxilla.

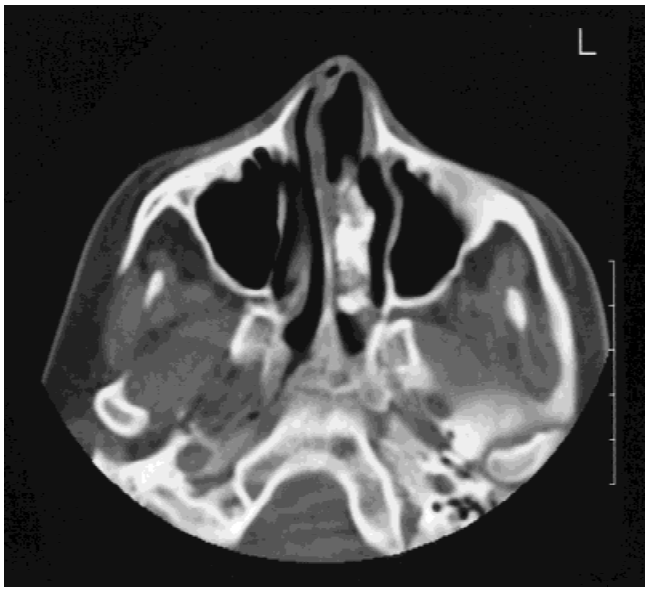

Fig. 2. CT scan of the sinuses of Case 2, showing a tumor mass extending from the anterior nasal region with a protrusion to the posterior side.

cobalt-60 radiation therapy of his right eye. A cataract developed later, and reduced vision in his right eye to 1/20.

He was seen 16 and a half years after the first diagnosis of bilateral retinoblastoma with a history of epistaxis, itching and feeling of a small mass in the nose since three weeks. A CT-scan of the sinuses showed a tumor mass extending from the anterior nasal region with a protrusion to the posterior side (Fig. 2). A MRI revealed an invasion of the right nasal fossa as well as of the maxillary and frontal sinuses. No metastases were demonstrated on chest X-ray examination or on CT-scan of the thorax. He had a biopsy of the tumor mass, that confirmed the diagnosis of osteosarcoma. He was treated with the same chemotherapy protocol as Case 1. A complete excision of the tumor mass was performed after three courses chemotherapy. Chromosomal abnormalities were not detected on southern blot (see materials and methods). He is well with no evidence of disease 5 years 7 months following the diagnosis of osteosarcoma.

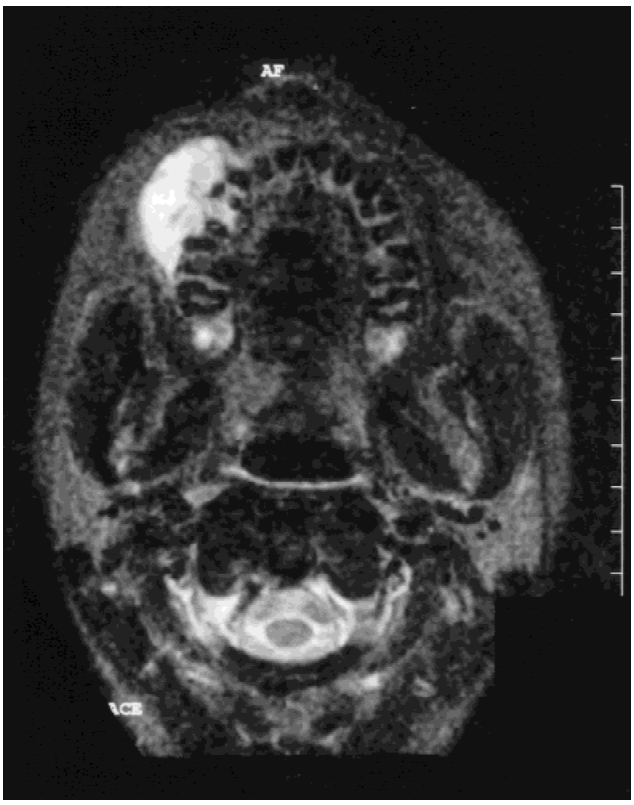

Fig. 3. MRI of the maxilla of Case 3, showing a tumor mass of 3 × 1.3 cm against the external cortex of the right superior maxilla with small lesions in the cortical area.

Case 3. A 14 year old girl, with no relevant history, was admitted to another hospital for a painless soft-tissue mass of the right cheek that grew rapidly. Plain radiographs of the maxilla and jaw revealed an irregular enlargement of the desmodental space between teeth 14 and 15. MRI of the maxilla showed a tumor mass of 3 × 1.3 cm against the external cortex of the right maxilla with small lesions in the cortical area (Fig. 3), and a MDP bone scintigraphy showed local increased activity. Chest X-ray films were normal. The patient had a biopsy of the tumor mass of the right maxilla; the diagnosis was osteosarcoma (Fig. 4). She was then referred to our hospital and was treated with the same chemotherapy protocol as Case 1. A complete excision of the right maxillary

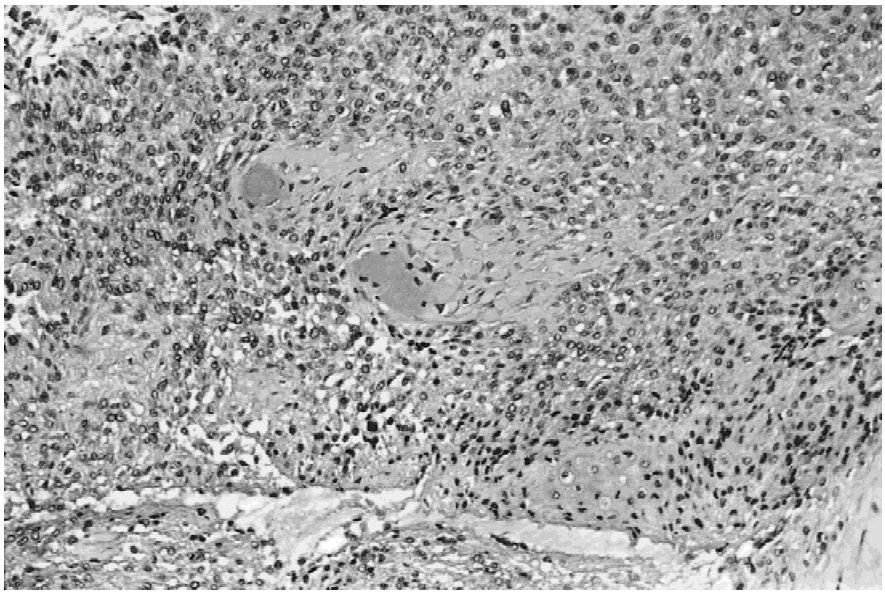

Fig. 4. Case 3: Photomicrograph showing a cellular tumor with proliferation of non-cohesive cells having an irregular round or spindle cell pattern with little pleomorphism and scanty mitoses. Nuclei are generally round or ovoid with granular chromatin and prominent nucleolus. Atypical cartilage is also present together with formation of osteoid (at the center). (H&E, ×32).

tumor mass followed by reconstruction of the defect with the temporal muscle was performed after three courses of chemotherapy. She is alive and well with no evidence of disease, 7 months from diagnosis.

MATERIALS AND METHODS

DNA was isolated from a set of tumors from unrelated patients each of the tumors was thought to arise because of inactivating mutations at the Rb locus. Screening of tumor DNA samples was performed by Southern blot analysis and probes derived from plasmid p4.95BT were used. Preliminary mapping was performed by ordering the genomic Hind III restriction endonuclease fragments present in normal DNAs that are reactive with this probe. An EcoRI/KpnI digest gives fragments that are 1.15 kb (5′KpnI-EcoRI fragment), 3.8 kb (3′EcoRI fragment), and 3.0 kb (Bluescript vector). DNA isolation, restriction endonuclease digestion of DNA samples, agarose gel electrophoresis, Southern blotting and hybridization were all performed according to standard methods.

DISCUSSION

Bone sarcomas are among the most common second malignant neoplasms (SMN) in childhood [2]. The tumor presents with focal bony destruction and invasion and often with distant metastases to the lung [3]. Both radiation therapy and chemotherapy with alkylating agents have been shown to increase the risk of subsequent development of secondary bone sarcomas in children who survive childhood cancers [4].

Retinoblastoma is a childhood malignant neoplasm occurring in 1/15000 to 1/30000 live births with a long term survival of more than 90% after successful treatment [5]. Retinoblastoma occurs in a genetic and sporadic form and is bilateral or unilateral. Approximately 75% of retinoblastomas are unilateral, but 98% of SMN occur in patients with bilateral retinoblastoma, as in our two patients, or in the 15% with unilateral retinoblastoma who harbor the germinal mutation [6]. Bilateral retinoblastoma is associated with the genetic form characterized by a deletion in the long arm of chromosome 13 (13q14) [7]. Ninety percent of retinoblastoma patients who develop a SMN have chromosome 13q14 deletion, identified as the tumor suppressor gene RB1 [8,9]. There is also ample evidence for a predisposition to retinoblastoma and osteosarcoma in individuals with altered RB1 gene and after making the assumption that children with retinoblastoma in whom osteosarcoma develop carry the gene [10]. Our two patients with secondary osteosarcoma were likely to have no chromosomal abnormalities on southern blot technique, however a complete sequencing in search of the RB1 gene was not performed. Low rates of mutation detection in large groups of patients are not unique to the RB1 gene. They reflect the difficulties in mutation analysis of large genes with an extensive mutational heterogeneity, resulting from the fact that not all mutations are detected by current mutation scanning techniques. Recently Lohmann and coll. (1996) reported the spectrum of RB1 germ-line mutations in 119 patients

with hereditary retinoblastoma [11]. Southern blot hybridization revealed mutations in 48 patients. By applying heteroduplex analysis, nonisotopic SSCP and direct sequencing, they detected mutations in 51 patients of the remaining 71. For the entire series of 119 patients, mutations were identified in 99 (83%).

For survivors of bilateral retinoblastoma, it has been suggested that the risk of SMN is 32%. When they also received radiation therapy, the SMN occurred for 70% in the field and for 30% outside the field of radiation [6]. Among survivors of hereditary retinoblastoma, osteosarcomas are diagnosed 2000 times more frequently in the skull after radiotherapy and 500 times more frequently in the extremities than would be expected in the general population [8]. In patients with hereditary retinoblastoma the most common SMNs have been osteogenic sarcomas. The second most frequent SMNs have been soft tissue sarcomas [12] and less commonly Ewing sarcoma, skin carcinoma, melanoma, acute lymphoblastic leukaemia and sinonasal carcinoma [13,14].

More than forty years ago, it was already known that sarcomas may arise in irradiated bones and more than 400 cases were described in the literature [15,16,17]. More than 100 cases of radiation-induced osteosarcomas of the orbit and face in retinoblastoma patients are known at the present time: François in 1977 reviewed 70 cases from the literature [18], Draper G.J. and coll. in 1986 reported 8 cases [12] and Newton et al. 1991 18 cases [19]. Kassir and coll. reported in 1997 a meta-analysis of 173 patients with osteosarcoma of the head and neck in nonrandomized studies [20].

It is also well known that treatment by alkylating agents may cause subsequent cancers. Draper et al. raise the possibility that cyclophosphamide may be responsible for the induction of SMN in retinoblastoma patients, and suggest that those carrying the retinoblastoma gene would be particularly susceptible to the carcinogenic effects both of radiation and cyclophosphamide [12].

The anthracyclines doxorubicin and daunorubicin are also known to be carcinogenic in vivo [21] and induce malignant transformation and mutations in vitro [22]. Newton and coll. [19] suggest that anthracyclines may increase the risk of one or more types of SMN and their data suggest also a synergistic effect of anthracyclines and alkylating agents combined. Two of our patients (case 1 & 2) had been treated with radiation for a primary bilateral retinoblastoma after which an osteosarcoma developed within the field of radiation after a prolonged asymptomatic period. There was a 5-year difference between the latency periods for the child who had received radiation alone and the one who had received radiation and chemotherapy, respectively 16 and 11 years, suggesting that the use of anthracyclines may have shortened the interval.

Our third patient (Case 3) presented with a primary osteosarcoma of the right maxilla. It is to be remembered that osteogenic sarcoma of the face is one of the rarest tumors encountered in childhood oncology. Huvos in 1979 reported approximately 412 published cases of osteogenic sarcoma of craniofacial bones in the literature [23]. Age and sex distribution in those patients reveals that only 6.3% of the osteosarcoma of the face occurs in the maxilla of girls between the age of 10 to 19 years. Even more striking is that only 0.45% of the osteogenic sarcoma were to be found in the maxilla of teenage girls, this in accordance with the skeletal location of osteogenic sarcoma in 605 cases [23]. Kassir and coll. tried in a recent meta-analysis of osteosarcoma of the head and neck to assess the role of adjuvant therapy in their treatment. The overall 5-year survival was 37%. The median survival for all patients was 30 months. Those with mandibular and maxillary tumors had similar survival rates; both groups fared significantly better than patients with extragnatic tumors ($P < 0.001$).

The mainstay of therapy is surgical resection with negative margins. Areas in the head and neck where this is especially difficult include extragnathic sites. Patients with these tumors had significantly decreased survival. These results are in accordance with the report of the head and neck sarcoma registry (which includes also soft tissue sarcomas) by Wanebo and coll. (1992) [24]. The worst survival, <45% at 5 years, occurred in patients with osteosarcoma, angiosarcoma and rhabdomyosarcoma in decreasing order.

While there have been encouraging results with adjuvant treatment protocols for long bone osteosarcoma, the ultimate role of radiation and chemotherapy in the management of osteosarcoma of the head and neck remains unproven. Nevertheless, we recommended that adjuvant therapy be considered due to the poor prognosis for osteosarcoma of the head and neck.

In conclusion, the prevalence of secondary osteosarcoma is increasing as the survival of patients who have childhood malignant lesions, such as retinoblastoma, increases. Although the reduction in radiation doses for retinoblastoma may reduce the number of subsequent osteogenic sarcomas, the effects of predisposing genes may become more apparent as more children survive for longer periods. The follow up of retinoblastoma survivors is imperative as well as molecular studies to detect individuals who are genetically predisposed and therefore more susceptible to SMN. Osteosarcoma of the head and neck, especially primary forms, remains a rare and highly malignant tumor demanding aggressive therapy. The best chance for cure still depends largely on radical surgical removal without residual disease at the margins. The ultimate role of radiation and chemotherapy remains

unproven but adjuvant therapy should be considered due to the poor prognosis in osteosarcoma of the face.

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